Recommended by Doctor of Medicine, Professor A. I. Bereznyakova

UDC 001.891.5:575.113:577.12-035.237.1(477) https://doi.org/10.24959/nphj.18.2204

M. M. Kobets, O. V. Filiptsova, Yu. M. Kobets

National University of Pharmacy

A social significance of the pharmacogenetic testing in Ukraine on the example of the *CYP2B6* gene participating in the nicotine metabolism

The study of the pharmacogenetic testing in Ukraine on the example of the gene *CYP2B6* participating in the nicotine metabolism is currently topical and socially significant problem.

Aim. To determine the potential sample among the residents of Ukraine, for which the therapeutic effect of the treatment of nicotine addiction with bupropion will be the most effective considering polymorphism of the *CYP2B6* gene.

Materials and methods. Genotyping of the participants in the study with respect to *CYP2B6* polymorphism (*rs3745274*) was carried out using a polymerase chain reaction. In addition to genotyping, the survey participants filled in questionnaires that reflected their socio-demographic data, as well as the lifestyle, duration and frequency of smoking.

Results and discussion. In the course of the studies conducted it has been found that approximately 7 % of the population has a genetic variant of *CYP2B6* predisposing to smoking. The same persons are a potential target audience for conducting the personalized therapy.

Conclusions. Prior the pharmacotherapy it is advisable to conduct the pharmacogenetic testing, which will reduce the cost of therapy and the risk of side effects in the future.

***Key words**: Pharmacogenetic testing; CYP2B6 gene; nicotine addiction; Ukraine*

М. М. Кобець, О. В. Філіпцова, Ю. М. Кобець

Соціальна значущість проведення фармакогенетичного тестування в Україні на прикладі гена *CYP2B6,* що бере участь у метаболізмі нікотину

Вивчення проведення фармакогенетичного тестування в Україні на прикладі гена *CYP2B6*, який бере участь у метаболізмі нікотину, є актуальною і соціально значущою проблемою.

Мета. Визначення потенційної вибірки серед жителів України, для якої терапевтичний ефект лікування нікотинової залежності бупропіоном буде найбільш ефективним з урахуванням поліморфізму гена *CYP2B6*.

Матеріали та методи. Генотипування учасників дослідження щодо поліморфізму *CYP2B6* (*rs3745274*) здійснювалося з використанням полімеразної ланцюгової реакції. Крім генотипування учасники дослідження заповнювали анкети, в яких були відображені їх соціодемографічні дані, а також особливості способу життя, тривалості та частоти паління.

Результати та їх обговорення. В ході проведених досліджень встановлено, що приблизно 7 % населення має генетичний варіант *CYP2B6*, який сприяє палінню. Ці ж особи є потенційною цільовою аудиторією для проведення персоналізованої терапії.

Висновки. Доцільним для призначення фармакотерапії є проведення фармакогенетичного тестування, що в подальшому дозволить знизити вартість лікування і ризик розвитку побічних ефектів.

***Ключові слова**: фармакогенетичне тестування; ген CYP2B6; нікотинова залежність; Україна*

М. Н. Кобец, О. В. Филипцова, Ю. Н. Кобец

Социальная значимость проведения фармакогенетического тестирования в Украине на примере гена *CYP2B6,* участвующего в метаболизме никотина

Изучение проведения фармакогенетического тестирования в Украине на примере гена *CYP2B6*, участвующего в метаболизме никотина, является актуальной и социально значимой проблемой.

Цель. Определение потенциальной выборки среди жителей Украины, для которой терапевтический эффект лечения никотиновой зависимости бупропионом будет наиболее эффективным с учетом полиморфизма гена *CYP2B6*.

Материалы и методы. Генотипирование участников исследования в отношении полиморфизма *CYP2B6* (*rs3745274*) осуществлялось с использованием полимеразной цепной реакции. Кроме генотипирования участники исследования заполняли анкеты, в которых были отражены их социодемографические данные, а также особенности образа жизни, длительности и частоты курения.

Результаты и их обсуждение. В ходе проведенных исследований установлено, что примерно 7 % населения имеет генетический вариант *CYP2B6*, предрасполагающий к курению. Эти же лица являются потенциальной целевой аудиторией для проведения персонализированной терапии.

Выводы. Целесообразным для назначения фармакотерапии является проведение фармакогенетического тестирования, что в дальнейшем позволит снизить стоимость лечения и риск развития побочных эффектов.

***Ключевые слова**: фармакогенетическое тестирование; ген CYP2B6; никотиновая зависимость; Украина*

In order to increase the effectiveness and safety of pharmacotherapy the pharmacogenetic testing is actively introduced into medical practice; it is based on the individual selection of drugs and their doses for a particular patient taking into account its genetic characteristics, including those associated with the metabolism of drugs. In particular, genetic peculiarities of patients are based on polymorphism of genes, which are encoding biotransformation enzymes and participating in pharmacokinetic and pharmacodynamic processes. Based on the results of the pharmacogenetic test a physician provides recommendations on the choice of drugs and their doses for a specific patient considering identification of his or her genotypes, which affect the pharmacological response [1].

Typically, patients can be divided as slow, intermediate and rapid metabolizers of drugs. In a slow metabolism of drugs there are side effects associated with the accumulation of drugs in the body. At the same time, higher concentrations of drugs in the blood are obtained during the treatment. The presence of alleles associated with a rapid metabolism of drugs in patients is characterized by the absence of a therapeutic concentration of drugs in the blood plasma and the risk of development of the therapeutic stability. Nowadays, the study of cytochrome P-450 isoenzymes involved in biotransformation of many prescribed and used drugs has become very popular [2].

A special role is played by polymorphism; information about it can be used for a large part of the population in connection with the prevalence of a disease or condition associated with it. One of the examples is nicotine addiction [3]. It is a serious social problem in society.

According to the World Health Organization (WHO), more than 7 million people die each year from tobacco addiction. More than 6 million of these deaths are the result of direct consumption of tobacco, and about 890.000 deaths occur among non-smokers exposed to secondhand smoke. Almost 80 % of more than 1 billion smokers in the world live in low- and middle-income countries. Unfortunately, due to the active distribution of hookahs and the increase in the number of smokers by 2030, the number of deaths due to smoking can grow to 8 million people. According to the latest WHO data, 1.3 billion of the world's population suffers from nicotine addiction, among them 12 % are female smokers [4].

There are different approaches to the pharmacotherapy of nicotine addiction in the world [5, 6, 7]. Thus, the authors studied the review of services for the therapy of tobacco addiction in 121 countries [8]. According to the prescriptions [7], one of the most effective methods for treating nicotine addiction is monotherapy and combined nicotine replacement pharmacotherapy. To treat nicotine addiction the following pharmacotherapeutic groups are used: drugs for the treatment of nicotine addiction N07BA01 (nicotine), N07BA (cytisine), N07B A03 (varenicline); N06AX12 (antidepressants, in particular bupropion); C02AC01 (imidazoline receptor agonists, in particular clonidine) [9].

However, such pharmacotherapy of nicotine addiction has not shown sufficient effectiveness. Recently, one of the most effective is the approach based on the classical principles of the personalized medicine [10].

In this regard, the use of antidepressants with the active substance bupropion ("Velbutrin" and "Zyban") is promising. It can be noted that both bupropion and nicotine are metabolized by the same enzyme – *CYP2B6*. Despite the fact that the role of *CYP2B6* in the metabolism of nicotine is great, other enzymes also participate in the metabolism of this substance. However, most of the studies is devoted to *CYP2B6*. In general, the *CYP2B6* gene has a great clinical importance and in addition to the metabolism of nicotine is involved in the metabolism of a number of widely used drugs, including cyclophosphamide, bupropion, methadone, efavirenz, ketamine, etc.

The studies conducted in the United States have shown that such treatment is the most effective for slow metabolizers since the longer action of bupropion in the body leads to a more pronounced therapeutic effect.

Thus, in one study 426 smokers of European descent with the experience of smoking at least 10 years, who decided to give up smoking, were prescribed antidepressants (bupropion 300 mg/day for 10 weeks or placebo) used to treat nicotine addiction. Each participant in the study was sampled for genotypes by *CYP2B6*. The analysis has shown that smokers with the decreased activity of the *CYP2B6* gene are more difficult to get rid of nicotine addiction than individuals with a normal form of this gene. However, the effectiveness of the antidepressant therapy was much higher than that of smokers with the reduced activity of this gene [10]. This is because the drug, which is the substrate of this enzyme, has a longer therapeutic effect.

The aim of the work is to determine the potential sample among the residents of Ukraine, for which the therapeutic effect of the treatment of nicotine addiction with bupropion will be the most effective considering polymorphism of the *CYP2B6* gene.

Materials and methods

Genotyping of the participants in the study with respect to *CYP2B6* polymorphism (*rs3745274*) was carried out using a polymerase chain reaction. It was performed earlier [11].

DNA was isolated from samples of the buccal epithelium using Chelex-100 ion exchange resin [12]. The allelic state of the *CYP2B6*6* gene was determined by the single nucleotide substitution of *516G/T* (*rs3745274*) according to the procedure [13]. Amplification was performed on a "Terzik" thermocycler.

Such oligonucleotide primers as AGGTGACAGCCTGATGTTCC and reverse TTTCTCGTGTGTTCTGGGTG were used to amplify the fragment of the *CYP2B6* gene that contained the polymorphic site (*516G/T*) [13]. Restriction of the amplification products was performed with BseNI endonuclease (MBI Fermentas, Lithuania). The restriction products were analyzed by electrophoresis in 2 % agarose gel. The molecular weight marker was pUC19 DNA hydrolyzed with *MspI* endonuclease (MBI Fermentas, Lithuania). Visualization of the amplification and restriction products was carried out by staining the gel with ethidium bromide and photographing

with a transiluminator in ultraviolet light. The restriction fragment with the size of 289 bp. corresponded to the TT genotype of variant *516G/T* of the *CYP2B6* gene, and two restriction fragments with the size of 196 and 93 bp. corresponded to the *GG* genotype. The presence of all three bands on the electrophoregram indicated the heterozygous *TG* genotype [13].

In addition to genotyping, the survey participants filled in questionnaires that reflected their socio-demographic data, as well as the lifestyle, duration and frequency of smoking. Participants in the study were not related to each other. For the current analysis, only some of the questions of the main part of the questionnaire were used. The personal information was collected taking into account ethical requirements when working with a human. All participants in the study gave their informed consent to an anonymous questionnaire. The relationship between qualitative characteristics was assessed using the χ^2 criterion. The conclusion on statistical hypotheses was made at the significance level of $p \leq 0.05$. The database was created in Microsoft Excel. Calculations were performed using Microsoft Excel and Statistica 6.

Results and discussion

The clinical significance of the *CYP2B6*6* variant of the *CYP2B6* gene stipulated to study the population distribution of the *516G/T* variant in the sample of the Ukrainian population. This study was pilot, and it was conducted in Ukraine for the first time. The biomaterial was samples of the buccal epithelium of 102 Ukrainians (54 females, 48 males). The distribution of genotypes in the sample of the population of Ukraine was determined by *516G/T* polymorphism of the *CYP2B6* gene: *GG* – in 56 % of the population, *GT* – in 37 %, and *TT* – in 7 % (Table).

The population frequencies of *516G/T* polymorphism of the *CYP2B6* gene are $p_G = 0.5$ and $q_T = 0.5$. The population structure did not deviate from the Hardy-Weinberg equilibrium.

On the other hand, the questionnaire information of the respondents made it possible to identify smokers (16 %) and non-smokers (84 %) among all genotyped participants. The studies by other Ukrainian authors have shown that, in general, the number of smokers is larger than in our data presented. In particular, approximately 40 % of men and 10 % of women smoke in Ukraine [14].

Table

Distribution of genotypes of *516G/T* polymorphism of the *CYP2B6* gene

Gender of the persons examined	Genotypes		
	GG	*GT*	*TT*
Male, *n*	27	16	5
Female, *n*	30	22	2
Total, %	56	37	7
Statistics: $\chi^2 = 0{,}656$, $df = 2$, $p > 0{,}05$.			

Note. χ^2 – Pearson's criterion; *df* – degree of freedom, *p* – level of significance.

Apparently, the underestimated number of smokers in the current sample is due to the relatively young age of those surveyed. For example, the youngest smoker is 17 years old, and the oldest – 30.

The data of another study are closer to our results obtained. Thus, according to the Kyiv International Institute of Sociology, among the residents of Ukraine, the prevalence of daily smoking is 24 % among persons aged 18 years, including 9 % among females and 42 % among males [14].

In the course of our study it has been found that 7 % of individuals are slow metabolizers (*GT*), in whom nicotine is metabolized slowly, and they are more prone to nicotine addiction, making up the corresponding risk group. The fast metabolizers (*GG*) among the subjects examined are 56 %. Due to the shorter time of the nicotine presence in their neurons the probability of the metabolism rearrangement in the cell and occurrence of nicotine addiction is reduced. Consequently, these individuals can most effectively get rid of nicotine addiction without the therapeutic intervention. This result is encouraging since for most Ukrainians, who do not have physical addiction, the explanatory work and aggressive advertising can be a sufficient incentive to stop smoking.

The approximate assessment of reasonability of the personalized and non-personalized approaches to therapy was conducted with and without pharmacogenetic testing. Based on the calculation that the duration of pharmacotherapy with "Zyban" drug was from 6 to 12 months the estimated price for the course of therapy was calculated. Information on the price for this drug was obtained as a result of the Internet search in various pharmacy chains in Ukraine [15]. As of December 28, 2017, the cost of "Zyban" tablets No. 30 was 2400 UAH or 85.4 USD, the cost of "Zyban" tablet No. 60 – 5200 UAH or 185 USD. Therefore, the cost of treatment is from 512.4 USD for 6 months to 1024.8 USD for 12 months. However, taking into account that this drug is effective only for a certain contingent and its relatively high cost it is highly desirable to perform pre-genotyping of individuals who are supposed to be treated with "Zyban". Based on our data this drug is theoretically effective only for approximately for 7 % of individuals.

Many pharmacogenetic studies in Ukraine are not conducted, but are possible outside of it. Abroad, in case of individual analysis, the cost of such genotyping is from 50 USD to 100 USD per sample [16]. In Ukraine, however, the cost of pharmacogenetic tests in general remains relatively high. Thus, in the laboratory of "Sinevo" network a similar study is included in the price list, but it is performed in Germany [16]. Unfortunately, the information presented on the site does not indicate what polymorphism is being investigated. The cost of *CYP2D6* genotyping is 12630 UAH, which is equivalent to 450 USD. Nevertheless, such studies are conducted once; they are the basis for subsequent medicinal prescriptions and are generally economically expedient. The example described clearly demonstrates the importance, feasibility and

social significance of pharmacogenetic testing before starting the individual therapy.

CONCLUSIONS

1. The social importance of the pharmacogenetic testing in Ukraine has been studied on the example of the *CYP2B6* gene. In Ukraine, 7 % of people are prone to smoking due to the characteristics of the *CYP2B6* genotype, and at the same time, they are a potential target audience for conducting the personalized therapy.

2. Prior the pharmacotherapy it is advisable to conduct the pharmacogenetic testing, which will reduce the cost of therapy and the risk of potential side effects.

Conflict of Interests: authors have no conflict of interests to declare.

REFERENCES

1. Сычев, Д. А. Фармакогенетическое тестирование : клиническая интерпретация результатов : реком. для практикующих врачей / Д. А. Сычев. – М., 2011. – 88 с.
2. Клиническая фармакогенетика / Д. А. Сычев, И. В. Игнатьев, Г. В. Раменская, В. Г. Кукес ; под ред. В. Г. Кукеса, Н. П. Бочкова. – М. : ГЭОТАР–МЕДИА, 2007. – 248 с.
3. 'Smoking genes': a genetic association study / Z. Verde, C. Santiago, J. M. Rodriguez Gonzalez–Moro et al. // PLoS One. – 2011. – Vol. 6, Issue 10. – e26668 p. doi: 10.1371/journal.pone.0026668
4. Website of the World Health Organization. – Available at : http://www.who.int/mediacentre/factsheets/fs339/en/
5. CYP2B6 rs2279343 polymorphism is associated with smoking cessation success in bupropion therapy / P. R. X. Tomaz, J. R. Santos, J. S. Issa et al. // Eur. J. Clin. Pharmacol. – 2015. – Vol. 71, Issue 9. – P. 1067–1073. doi: 10.1007/s00228–015–1896–x
6. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation : a randomized clinical trial / C. F. Koegelenberg, F. Noor, E. D. Bateman et al. // JAMA. – Vol. 312, Issue 2. – 155 p. – doi: 10.1001/jama.2014.7195
7. Elrashidi, M. Y. Emerging drugs for the treatment of tobacco dependence : 2014 update / M. Y. Elrashidi, J. O. Ebbert // Expert opinion on emerging drugs. – 2014. – Vol. 19, Issue 2. – P. 243–260. doi: 10.1517/14728214.2014.899580
8. A survey of tobacco dependence treatment services in 121 countries / H. Pine–Abata, A. McNeill, R. Murray et al. // Addiction. – 2013. – Vol. 108, Issue 8. – P. 1476–1484. doi: 10.1111/add.12172
9. Pharmacotherapy for Nicotine/Tobacco Use Dependence / D. Elbe, K. Z. Bezchlibnyk–Butler, A. S. Virani, R. M. Procyshyn // Clinical Handbook of Psychotropic Drugs for Children and Adolescents. – 3-d. – Hogrefe Publishing, 2014. – 329 p.
10. Pharmacogenetic investigation of smoking cessation treatment / C. Lerman, P. G. Shields, E. P. Wileyto et al. // Pharmacogenetics. – 2002. – Vol. 12, Issue 8. – P. 627–634. doi: 10.1097/00008571–200211000–00007
11. SNP polymorphism of CYP1A2 (rs762551) and CYP2B6 (rs3745274) in the Ukrainian population : a pilot study / O. V. Filiptsova, M. N. Kobets, Yu. N. Kobets, I. A. Timoshyna // From genomics to therapy. – Barcelona, Spain, 2017. – 80 p.
12. Walsh, P. S. Chelex 100 as a medium for extraction of DNA for PCR–based typing from forensic material / P. S. Walsh, D. A. Metzger, R. Higuchi // BioTechniques. – 1991. – Vol. 10. – P. 506–513.
13. Prevalence of MDR1 C3435T and CYP2B6 G516T Polymorphisms among HIV–1 Infected South African Patients / T. M. Masebe, P. O. Bessong, J. Nwobegahay et al. // Dis Markers. – 2012. – Vol. 32, Issue 1. – P. 43–50. doi: 10.1155/2012/453479
14. Число курильщиков в Украине стабилизировалось на уровне 24 %. – Режим доступа: https://zn.ua/UKRAINE/chislo–kurilschikov–v–ukraine–stabilizirovalos–na–urovne–24–202795_.html
15. Справочная аптек. – Режим доступа: https://www.spravka–apteka.com.ua/ziban–price/
16. All tests – take tests in medical laboratory «Synevo». – Available at: https://www.synevo.ua/en/analizy/vse–analizy/

REFERENCES

1. Sychev, D. A. (2011). *Farmakogeneticheskoe testirovanie: klinicheskaia interpretatciia rezultatov*. Moscow, 88.
2. Sychev, D. A., Ignatev, I. V., Ramenskaia, G. V., Kukes, V. G. (2007). *Klinicheskaia farmakogenetika*. Moscow: GEOTAR–MEDIA, 248.
3. Verde, Z., Santiago, C., Rodríguez González–Moro, J. M., de Lucas Ramos, P., López Martín, S., Bandrés, F., Gómez–Gallego, F. (2011). "Smoking Genes": A Genetic Association Study. *PLoS ONE, 6 (10)*, e26668. doi: 10.1371/journal.pone.0026668
4. Website of the World Health Organization. Available at: http://www.who.int/mediacentre/factsheets/fs339/en/
5. Tomaz, P. R. X., Santos, J. R., Issa, J. S., Abe, T. O., Gaya, P. V., Krieger, J. E., Santos, P. C. J. L. (2015). CYP2B6 rs2279343 polymorphism is associated with smoking cessation success in bupropion therapy. *European Journal of Clinical Pharmacology, 71 (9)*, 1067–1073. doi: 10.1007/s00228–015–1896–x
6. Koegelenberg, C. F. N., Noor, F., Bateman, E. D., van Zyl–Smit, R. N., Bruning, A., O'Brien, J. A., Irusen, E. M. (2014). Efficacy of Varenicline Combined With Nicotine Replacement Therapy vs Varenicline Alone for Smoking Cessation. *JAMA, 312 (2)*, 155. doi: 10.1001/jama.2014.7195
7. Elrashidi, M. Y., Ebbert, J. O. (2014). Emerging drugs for the treatment of tobacco dependence: 2014 update. *Expert Opinion on Emerging Drugs, 19 (2)*, 243–260. doi: 10.1517/14728214.2014.899580
8. Piné–Abata, H., McNeill, A., Murray, R., Bitton, A., Rigotti, N., Raw, M. (2013). A survey of tobacco dependence treatment services in 121 countries. *Addiction, 108 (8)*, 1476–1484. doi: 10.1111/add.12172
9. Elbe, D., Bezchlibnyk–Butler, K. Z., Virani, A. S., Procyshyn, R. M. (2014). Pharmacotherapy for Nicotine/Tobacco Use Dependence. *Clinical Handbook of Psychotropic Drugs for Children and Adolescents, 3d*. Hogrefe Publishing, 329.
10. Lerman, C., Shields, P. G., Wileyto, E. P., Audrain, J., Pinto, A., Hawk, L., Epstein, L. (2002). Pharmacogenetic investigation of smoking cessation treatment. *Pharmacogenetics, 12 (8)*, 627–634. doi: 10.1097/00008571–200211000–00007
11. Filiptsova, O. V., Kobets, M. N., Kobets, Yu. N, Timoshyna, I. A. (2017). SNP polymorphism of CYP1A2 (rs762551) and CYP2B6 (rs3745274) in the Ukrainian population: a pilot study. *From genomics to therapy.* Barcelona, Spain, 80.

12. Walsh, P. S., Metzger, D. A., Higuchi, R. (1991). Chelex 100 as a medium for extraction of DNA for PCR–based typing from forensic material. *BioTechniques, 10*, 506–513.
13. Masebe, T. M., Bessong, P. O., Nwobegahay, J., Ndip, R. N., Meyer, D. (2012). Prevalence of MDR1 C3435T and CYP2B6 G516T Polymorphisms among HIV–1 Infected South African Patients. *Disease Markers, 32 (1)*, 43–50. doi: 10.1155/2012/453479
14. *Chislo kurilshchikov v Ukraine stabilizirovalos na urovne 24%*. Available at: https://zn.ua/UKRAINE/chislo–kurilschikov–v–ukraine–stabilizirovalos–na–urovne–24–202795_.html
15. *Spravochnaia aptek*. Available at: https://www.spravka–apteka.com.ua/ziban–price/
16. *All tests – take tests in medical laboratory "Synevo"*. Available at: https://www.synevo.ua/en/analizy/vse–analizy/

Information about authors:
Kobets M. M., Candidate of Pharmacy (PhD), assistant professor of the Department of Pharmaceutical Marketing and Management, National University of Pharmacy. E-mail: maya4ok777@yahoo.com. ORCID: http://orcid.org/0000-0003-0736-0167
Filiptsova O. V., Doctor of Biology (Dr. habil.), professor, head of the Department of Biology, National University of Pharmacy. E-mail: philiptsova@yahoo.com. ORCID: http://orcid.org/0000-0002-1297-1651
Kobets Yu. M., Candidate of Pharmacy (PhD), assistant professor of the Department of Pharmaceutical Marketing and Management, National University of Pharmacy. E-mail: beretta98g@gmail.com. ORCID: http://orcid.org/0000-0002-3631-5018
Відомості про авторів:
Кобець М. М., канд. фарм. наук, доцент кафедри фармацевтичного маркетингу та менеджменту, Національний фармацевтичний університет. E-mail: maya4ok777@yahoo.com. ORCID: http://orcid.org/0000-0003-0736-0167
Філіпцова О. В., д-р біол. наук, професор, завідувач кафедри біології, Національний фармацевтичний університет. E-mail: philiptsova@yahoo.com. ORCID: http://orcid.org/0000-0002-1297-1651
Кобець Ю. М., канд. фарм. наук, доцент кафедри фармацевтичного маркетингу та менеджменту, Національний фармацевтичний університет. E-mail: beretta98g@gmail.com. ORCID: http://orcid.org/0000-0002-3631-5018
Сведения об авторах:
Кобец М. Н., канд. фарм. наук, доцент кафедры фармацевтического маркетинга и менеджмента, Национальный фармацевтический университет. E-mail: maya4ok777@yahoo.com. ORCID: http://orcid.org/0000-0003-0736-0167
Филипцова О. В., д-р биол. наук, профессор, заведующая кафедрой биологии, Национальный фармацевтический университет. E-mail: philiptsova@yahoo.com. ORCID: http://orcid.org/0000-0002-1297-1651
Кобец Ю. Н., канд. фарм. наук, доцент кафедры фармацевтического маркетинга и менеджмента, Национальный фармацевтический университет. E-mail: beretta98g@gmail.com. ORCID: http://orcid.org/0000-0002-3631-5018

Надійшла до редакції 21.11.2017 р.